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Low Dose Quinidine-Mexiletine Combination Therapy Versus Quinidine Monotherapy for Treatment of Ventricular Arrhythmias

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Low dose quinidine-mexiletine combination therapy was compared with quinidine monotherapy in 15 patients with frequent ventricular premature complexes and nonsustained ventricular tachycardia in a dose escalation crossover study. Oral combination therapy was initiated with quinidine gluconate (165 mg) plus mexiletine (150 mg) every 8 h. If ventricular premature complexes were not suppressed ≥80% and nonsustained ventricular tachycardia ≥90%, the dose was increased to a maximum of 330 mg of quinidine plus 200 mg of mexiletine. Quinidine monotherapy was initiated with 330 mg and escalated to a maximum of 660 mg every 8 h if criteria for effectiveness were not met.

Combination quinidine-mexiletine therapy suppressed 80% of ventricular premature complexes in 13 of 14 patients and suppressed 100% of episodes of ventricular tachycardia in 6 of 8 patients (mean quinidine dose 200 ± 70 mg; mean mexiletine dose 146 ± 24 mg every 8 h). The mean effective trough quinidine and mexiletine concentration was 1.0 ± 0.7 and 0.9 ± 0.4 μg/ml, respectively. Monotherapy was less effective; that is, ≥80% suppression of ventricular premature complexes was observed in 5 of 15 patients and 100% suppression of ventricular tachycardia in 2 of 9 patients. The mean quinidine monotherapy dose was 462 ± 155 mg every 8 h; the mean quinidine concentration was 1.8 ± 0.8 μg/ml.

Adverse systemic effects occurred in 3 patients on quinidine-mexiletine therapy and in 11 on quinidine monotherapy. Neither treatment prolonged PR or QRS intervals, but monotherapy prolonged the QTc interval ($p < 0.05$); both treatments prolonged the coupling interval ($p < 0.05$). Low dose quinidine-mexiletine is more effective and better tolerated than are standard doses of quinidine.

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Clinical reports (1–5) of the effectiveness of antiarrhythmic therapy note that combining agents with varied electrophysiologic properties often results in more profound antiarrhythmic action than does monotherapy. Quinidine-mexiletine has been shown (3–5) to be an effective combination against sustained ventricular tachycardia and inducible ventricular arrhythmias, even in patients refractory to monotherapy and at risk of sudden cardiac death. Perhaps because of their serious nature, sustained ventricular arrhythmias have been treated with relatively large doses of combination quinidine-mexiletine, equivalent to monotherapy. Theoretically, however, if quinidine and mexiletine are synergistic, lower doses used in combination should be more effective than monotherapy and associated with fewer adverse effects. This position is taken by the U.S. Food and Drug Administration when recommending approval of combination therapy. Accordingly, this project was initiated to compare the effect of the low end of the dose response for quinidine-mexiletine combination therapy with that of quinidine monotherapy on frequency of ventricular premature complexes and nonsustained ventricular tachycardia in patients with symptomatic arrhythmias.

It was our goal to 1) determine whether low dose combination treatment effectively suppresses arrhythmias; 2) evaluate the effect of quinidine-mexiletine combination therapy and quinidine monotherapy on arrhythmia frequency and the electrocardiogram (ECG); and 3) assess the frequency of adverse effects. To this end, 15 patients with symptomatic ventricular premature complexes were enrolled in a placebo-controlled, single-blind, randomized crossover trial. The protocol was implemented using a crossover design to minimize patient differences and, thus,

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each patient served as his or her own control during two active drug treatments.

Methods

Study design. The protocol was first approved by the Institutional Review Board of Columbia University on December 17, 1986 and last reapproved on November 16, 1988. After a screening visit, written informed consent was obtained, and patients had drug-free 24 h ambulatory ECG recordings, 12 lead ECG monitoring and blood chemistry determinations. At least 10 ventricular premature complexes/h documented on two 24 h ambulatory ECG recordings containing ≥20 h of interpretable recordings were required for enrollment. The protocol required discontinuation of all other antiarrhythmic drugs for at least 5 half-lives. Digitalis derivatives and beta-adrenergic blocking agents were continued if prescribed for treatment other than ventricular arrhythmias.

The study was divided into four stages: 1) pretreatment drug-free period; 2) dose escalation with combination therapy or monotherapy; 3) drug washout; and 4) dose escalation with the alternate active therapy. Patients were excluded if they had evidence of the following: 1) advanced atrioventricular (AV) block without a permanent pacemaker; 2) decompensated congestive heart failure; 3) a history of sudden cardiac death, syncope or sustained ventricular tachycardia; 4) known intolerance, previous lack of efficacy or previous proved efficacy with either drug; 5) myocardial infarction within 3 months of study; or 6) severe renal or hepatic disease.

Treatment. The end point for treatment was ≥80% suppression of ventricular premature complexes (6,7) and ≥90% suppression of nonsustained ventricular tachycardia (7). The first (lowest) dose of combination therapy was quinidine, 165 mg, plus mexiletine, 150 mg, given orally every 8 h. If <80% suppression of ventricular premature complexes occurred, the dose was increased to quinidine, 330 mg, plus mexiletine, 150 mg (mid dose), and then quinidine, 330 mg, plus mexiletine, 200 mg (highest dose). Mexiletine in capsules of 100 and 150 mg and quinidine gluconate tablets, each 330 mg (Warner-Chilcott), were provided by Boehringer-Ingelheim. The initial dose of oral quinidine gluconate (lowest dose) for monotherapy was 330 mg every 8 h, then 495 mg (mid dose) and was escalated to a maximum of 660 mg (highest dose) every 8 h if there was <80% suppression of ventricular premature complexes and treatment was tolerated. Patients received a dose for ≥72 h before obtaining a 24 h ambulatory ECG to evaluate its effect; at that time, the 12 lead ECG, blood chemistry values and drug concentration were also obtained.

Ambulatory 24 h ECG recordings. The ambulatory ECG was recorded during a drug-free period (2), during each dose escalation (1–3) and during washout (1). During dose escalation and washout, the ambulatory ECG was obtained after a minimum of 5 treatment or washout days. Ambulatory ECG recordings were obtained on Avionics 445B or 453 series two channel recorders and analyzed by the Ambulatory ECG Laboratory at Columbia University (8). Quality control in this laboratory has shown a correlation coefficient of 0.99 for ventricular premature complexes, 0.99 for ventricular couplets and 0.98 for runs of ventricular tachycardia. The effect of the first active treatment was compared with the drug-free 24 h ambulatory ECG and the second active treatment was compared with the washout recording.

Electrocardiographic intervals. The effect of treatment on ECG intervals was measured before and after combination and monotherapy. Measurement of the PR, QRS, QTc, RR and the coupling interval (RV) was made in leads II and V_2 or V_6. At least five measurements of each interval were made and the average determined. The QTc interval was determined using Bazett's formula: $QTc = QT/\sqrt{RR}$.

Serum drug concentrations. Steady-state trough serum samples were obtained at each tolerated dose of both treatments. Mexiletine was assayed by using a modification of a high performance liquid chromatographic method (9), and quinidine by using an enzymatic immunoassay (EMIT) (10).

Statistical analysis. Data are expressed as mean values ± 1 SD and median. A paired *t* test was used to compare drug concentrations, mean ECG intervals (PR, QRS, QTc, RV intervals), frequency of ventricular premature complexes, episodes of ventricular tachycardia and rate of ventricular tachycardia before and after each treatment, and to compare combination therapy with monotherapy. Regression analysis was used to determine the relation of pretreatment ventricular premature complexes to washout and the relation of quinidine dose to quinidine concentration. A p value <0.05 was considered significant.

Results

Clinical characteristics. The study group consisted of 15 patients (11 women, 4 men); 5 had cardiomyopathy, 5 had a primary electrical abnormality, 2 had ischemic heart disease, 2 had hypertensive heart disease and 1 had mitral valve prolapse. Ejection fraction was determined in 13 patients, either by radionuclide angiogram (n = 12) or by echocardiogram (n = 1). The mean pretreatment ejection fraction was 52% ± 14% (range 23% to 67%, median 55%). The mean pretreatment cardiothoracic ratio on the chest X-ray film for 14 patients was 0.51 ± 0.09. Ten patients were taking one or more cardiac medications: six an angiotensin-converting enzyme inhibitor, four a beta-blocker, three a digitalis glycoside, two a potassium supplement, one a calcium channel antagonist and one warfarin. None of the patients had previously been treated with quinidine or mexiletine, except one who had sporadically taken quinidine without proved efficacy.

JACC Vol. 15, No. 5
April 1990:1138–45

Table 1. Electrocardiographic Intervals in 15 Patients

	PR	QRS	QT_c	RV
Q + M (pre)	182 ± 27	92 ± 21	432 ± 29	476 ± 57
Q + M (post)	188 ± 22	91 ± 21	433 ± 28	531 ± 80*
Mean Δ	6	−1	1	55
Q (pre)	176 ± 20	89 ± 22	408 ± 35	476 ± 57
Q (post)	180 ± 24	91 ± 21	448 ± 44*	545 ± 51*
Mean Δ	4	2	40	69

*$p < 0.05$ predrug (pre) versus postdrug (post). All values are in ms. M = mexiletine; Q = quinidine; RV = coupling interval; Δ = change.

Electrocardiographic intervals. No significant difference was noted for pretreatment PR, QRS, QTc, RR or RV intervals before combination therapy or monotherapy (Table 1). No significant change from mean pretreatment PR or mean QRS intervals occurred after quinidine-mexiletine combination therapy or quinidine monotherapy. The pretreatment QTc interval did not change significantly after combination therapy and did not prolong to ≥500 ms. However, quinidine monotherapy prolonged the QTc interval significantly, from 408 ± 35 to 448 ± 44 ms ($p < 0.05$), and in two patients, the QTc interval prolonged to ≥500 ms. One patient developed first degree AV block during both treatments. In one patient atrial fibrillation converted to sinus rhythm during quinidine-mexiletine therapy; in this patient conversion had not occurred during the initial period of randomization to quinidine monotherapy.

The mean drug-free coupling interval (RV interval), measured in 12 patients, was 476 ± 57 ms. Quinidine-mexiletine combination therapy significantly ($p < 0.05$) prolonged the mean RV interval to 531 ± 80 ms, as did quinidine monotherapy (545 ± 51 ms, $p < 0.05$). No significant difference was found between the effect of quinidine-mexiletine combination therapy and monotherapy on the RV interval (Table 1).

Effect of quinidine-mexiletine on arrhythmia (Tables 2 and 3). There was no difference in the frequency of ventricular premature complexes before the patients received quinidine-mexiletine combination therapy or quinidine monotherapy (p = NS) (Fig. 1). Baseline frequency of ventricular premature complexes before quinidine-mexiletine combination therapy averaged 209 ± 327/h (range 12 to 1,263, median 121). Fourteen patients received quinidine-mexiletine therapy; 13 of these patients had >80% suppression of ventricular premature complexes and 1 patient had 59% suppression. After treatment, the mean frequency of ventricular premature complexes was 23 ± 33/h (range 1 to 104, median 17) ($p < 0.05$); the mean percent suppression was 88% ± 11 (median 93%) (Table 2).

There was no difference in the frequency of episodes of ventricular tachycardia before receiving quinidine-mexiletine combination therapy or quinidine monotherapy (p = NS). Eight patients receiving quinidine-mexiletine therapy had nonsustained ventricular tachycardia or ventricular rhythm (<100 beats/min) before treatment at a mean frequency of episodes of 277 ± 479 (range 1 to 1,060, median 7). After treatment, six of the eight patients had nonsustained ventricular tachycardia abolished; two others had 98% and 99% suppression ($p < 0.05$), respectively. The longest runs and the fastest rates of ventricular tachycardia decreased in these two patients (Table 3). The mean frequency of ventricular tachycardia episodes after treatment was 3 ± 9 (range 0 to 26, median 0), mean percent abolition 100 ± 1% (median 100%) ($p < 0.05$) (Table 3).

Effect of quinidine monotherapy on arrhythmias (Tables 2 and 3). Baseline frequency of ventricular premature complexes before administration of quinidine monotherapy averaged 248 ± 285/h (range 16 to 971, median 125). Five of the 15 patients who received quinidine monotherapy had >80% suppression of ventricular premature complexes; in 4 others the treatment had an antiarrhythmic effect but did not reach the 80% suppression criterion (range 69% to 74%). After treatment, the mean frequency of ventricular premature complexes was 129 ± 169/h (range 1 to 615, median 96) ($p < 0.05$); mean percent suppression was 52 ± 44% (range −45% to 98%, median 78%) (Table 2). The effect of quinidine-mexiletine combination therapy on the suppression of ventricular premature complexes was more marked than that of quinidine monotherapy ($p < 0.05$).

Nine patients had episodes of nonsustained ventricular tachycardia or ventricular rhythm before quinidine monotherapy (mean frequency 393 ± 905, range 1 to 2,762, median 8). After treatment, two had nonsustained ventricular tachycardia abolished. Quinidine shortened runs and slowed the rate of ventricular tachycardia in all but two patients ($p < 0.05$). One patient had a >10-fold increase in episodes of nonsustained ventricular tachycardia and was considered to have proarrhythmia; after treatment, the mean frequency of ventricular tachycardia episodes was 1,050 ± 2,928 (range 0 to 8,842, median 1); mean percent suppression was −150 ± 555% (range −1,607% to 100%, median 75%). Quinidine-mexiletine therapy was more effective than quinidine therapy in suppressing episodes of nonsustained ventricular tachycardia ($p < 0.05$).

Dose and drug concentration after combination therapy (Fig. 2). The mean dose of combination treatment in 14 patients was low: quinidine, 200 ± 70 mg, and mexiletine, 146 ± 24 mg every 8 h (Table 2). Ten of the 13 patients who responded to quinidine-mexiletine combination therapy did so at: quinidine, 165 mg, and mexiletine, 150 mg. One patient taking quinidine, 165 mg, had 80% suppression of ventricular premature complexes even after mexiletine was titrated down to 100 mg every 8 h; another responded to quinidine, 330 mg, and mexiletine, 150 mg; and another to quinidine, 330 mg, and mexiletine, 200 mg. The one patient who did not achieve 80% suppression had adverse effects with quinidine,

Table 2. Effect on Ventricular Premature Complexes and Episodes of Ventricular Tachycardia

Patient No.	Dose (mg)	VPC/h (pre)	VPC/h (post)	%	VT Episodes (pre)	VT Episodes (post)	%
			Quinidine-Mexiletine				
1	165/150	81	1	100	0	0	0
2	165/150	175	2	99	0	0	0
3	165/150	483	88	82	1,042	26	98
4	165/150	46	4	91	1	0	100
5	165/150	45	3	93	0	0	0
6	165/150	20	1	95	0	0	0
7	165/150	12	1	98	0	0	0
8	165/150	166	12	93	1	0	100
10	330/150	153	27	82	3	0	100
11	330/100	17	7	59	5	0	100
12	165/150	119	21	82	0	0	0
13	330/200	1,263	104	92	1,060	0	100
14	165/100	237	46	81	95	1	99
15	165/150	112	13	88	10	0	100
Mean	200/146	209	23*†	88	277	3‡	100
±SD	70/24	327	33	11	479	9	1
Median	165/150	121	17	93	7	0	100
			Quinidine				
1	330	57	6	89	0	0	0
2	495	94	122	−30	0	0	0
3	330	709	207	71	518	8,842	−1,607
4	330	38	6	84	1	2	−100
5	330	285	127	55	4	0	100
6	660	16	5	69	0	0	0
7	330	22	1	98	0	0	0
8	330	178	24	87	0	0	0
9	330§	508	131	74	0	0	0
10	495	153	222	−45	4	1	75
11	660	27	6	78	3	1	80
12	660	113	96	15	10	4	60
13	660	971	615	37	2,762	17	99
14	330	425	346	19	226	583	−158
15	660	125	24	83	8	0	100
Mean	462	248	129‖	52	393	1,050	−150
±SD	155	285	169	44	905	2,928	555
Median	330	125	96	78	8	1	75

*$p < 0.05$ = ventricular premature complexes (VPC) pre versus post quinidine-mexiletine; †$p < 0.05$ = ventricular premature complexes quinidine-mexiletine (post) versus quinidine (post); ‡$p < 0.05$ = ventricular tachycardia (VT) quinidine-mexiletine (post) versus quinidine (post); §patient received maximal dose of 660 mg every 8 h quinidine, but developed rash and could not have efficacy tested on this dose; ‖$p < 0.05$ = ventricular premature complexes pre versus post quinidine.

330 mg, and mexiletine, 100 mg. The effective trough quinidine concentration in combination with mexiletine was 1.0 ± 0.7 μg/ml (range 0 to 3.2), and trough mexiletine concentration was 0.9 ± 0.4 μg/ml (range 0.1 to 1.6). Figure 3 describes the log dose-probit curves and characterizes the dose-effect relation between quinidine and mexiletine.

Dose and drug concentration after monotherapy. The mean quinidine monotherapy dose in 15 patients was 462 ± 155 mg every 8 h (range 330 to 660, median 330) (Table 2) and the trough concentration was 1.8 ± 0.8 μg/ml. Seven of the patients taking quinidine, 330 mg, either responded (n = 4) or had adverse effects (n = 3). Eight patients who did not achieve 80% suppression after 330 mg required an increase in dose: one showed improvement but four did not after quinidine, 660 mg every 8 h. Adverse effects occurred in two patients who received quinidine, 495 mg, and one patient who received quinidine, 660 mg. The effective quinidine dose for the five patients with >80% suppression was 396 ±

JACC Vol. 15, No. 5
April 1990:1138–45

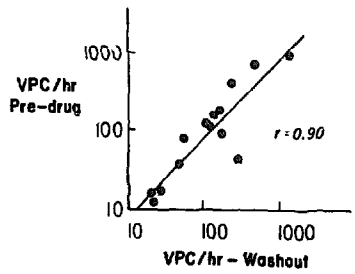
Table 3. Effect on Frequency and Rate of Ventricular Tachycardia

Patient No.	Pre-treatment			Post-treatment		
	Episodes	Longest VT ([no. of beats]/[beats/min])	Fastest VT ([no. of beats]/[beats/min])	Episodes	Longest VT ([no. of beats]/[beats/min])	Fastest VT ([no. of beats]/[beats/min])
			Quinidine-Mexiletine			
3	1,042	17/107	3/117	26	9/112	9/112
4	1	3/78	3/78	0	—	—
5	0	—	—	0	—	—
8	1	3/121	3/121	0	—	—
10	3	4/158	4/158	0	—	—
11	5	5/172	5/172	0	—	—
12	0	—	—	0	—	—
13	1,060	6/153	6/153	0	—	—
14	95	9/216	9/216	1	3/131	3/131
15	10	4/69	3/149	0	—	—
Mean	277	6/134	5/146	3*	6/122†	6/122‡
±SD	479	8/50	2/41	9	4/13	4/13
			Quinidine			
3	518	22/125	8/132	8,842	70/110	3/134
4	4	4/88	4/88	2	3/57	3/57
5	4	3/121	3/121	0	—	—
8	0	—	—	0	—	—
10	4	4/143	4/143	1	3/120	3/120
11	3	5/174	5/174	1	4/112	4/112
12	10	3/125	3/125	4	3/118	3/118
13	2,762	6/132	4/158	17	4/99	3/102
14	226	11/194	3/240	583	19/57	4/264
15	8	3/147	3/147	0	—	—
Mean	393	7/139	4/148	1,050	15/96§	3/121‖
±SD	905	6/31	2/42	2,928	25/28	0.5

*$p < 0.5$ = ventricular tachycardia (VT), quinidine-mexiletine (post) versus quinidine (post); †$p < 0.05$ = rate of longest ventricular tachycardia episode, quinidine-mexiletine pre versus post; ‡$p < 0.05$ = rate of fastest ventricular tachycardia episode, quinidine-mexiletine pre versus post; §$p < 0.05$ = rate of longest ventricular tachycardia episode, quinidine pre versus post; ‖$p < 0.05$ = rate of fastest ventricular tachycardia episode, quinidine pre versus post. Abbreviations as in Table 2.

148 mg every 8 h (range 330 to 660, median 330); the effective trough quinidine concentration was 1.7 ± 0.8 μg/ml (range 0.7 to 2.8). A linear relation between the quinidine dose and concentration ($r = 0.72$, $p < 0.05$) was observed. There was a significant difference between the quinidine concentration attained after combination versus monotherapy ($p < 0.05$). The average trough quinidine concentration in both treatment limbs was lower than the conventional therapeutic range (2 to 5 μg/ml). Precise timing of blood sampling after drug administration in a relatively small outpatient trial could have accounted for the low and variable quinidine concentrations. The effective quinidine concentration range after quinidine-mexiletine administration could be lower than the currently accepted therapeutic range, but this will require further evaluation.

Figure 1. Frequency of ventricular premature complexes (VPC) per hour (log scale) on the predrug versus washout 24 h ambulatory electrocardiogram. There is no difference between frequency during the two periods ($r = 0.90$).



Adverse systemic and cardiac effects (Table 4). One or more adverse systemic effects were attributed to combination quinidine-mexiletine, and therapy was discontinued in three patients because of headache, cough, insomnia, nervousness or dry mouth. In retrospect, cough may have been caused by concomitant therapy with a converting enzyme inhibitor. No adverse cardiac effects were noted during treatment with quinidine-mexiletine combination therapy.

During quinidine monotherapy, adverse systemic or car-

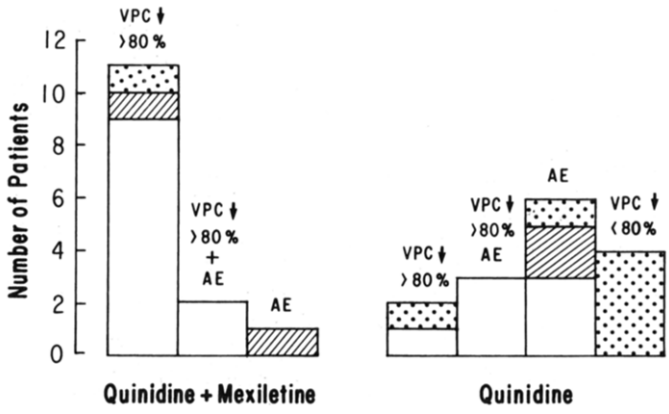


Figure 2. Frequency of responders (>80% suppression of ventricular premature complexes [VPC]), non responders (<80% suppression) and adverse events (AE) after quinidine-mexiletine (**left panel**) and quinidine monotherapy (**right panel**). Doses (see Methods) are either the effective or the maximal doses received. **Open bars** = lowest dose; **hatched bars** = mid dose; **dotted bars** = highest dose.

diac effects occurred in 11 of the 14 patients. One or more adverse systemic effects (nausea, diarrhea, headache, rash, fever, eye swelling and bloating) occurred in six patients. One or more adverse cardiac effects (increased palpitation, proarrhythmia, prolonged QTc interval and significant bradycardia [<30 beats/min]) occurred in four patients. A body rash observed in one patient prevented crossover to quinidine-mexiletine treatment. In patients taking the lowest quinidine monotherapy dose (330 mg every 8 h), 10 of 13 complaints were probably related to quinidine administration and 3 were doubtfully related.

Figure 3. The log dose-probit curves for *quinidine* in combination with mexiletine (**dotted and dashed line**), *mexiletine* in combination with quinidine (**solid line**) and *quinidine monotherapy* (**dashed line**) determined from patients with ≥80% suppression of ventricular premature complexes. The dose-response relation can be linearized using probit (for probability) transformations. The customary measure of potency (ED_{50}) is the point on the log dose scale corresponding to probit 5 (**left**) and 50% responding (**right**). The line describing the quinidine dose used in combination with mexiletine is left of the line describing quinidine monotherapy. From the theoretic line, the quinidine dose at which 50% respond after combination therapy is <100 mg and after monotherapy is >990 mg every 8 h.

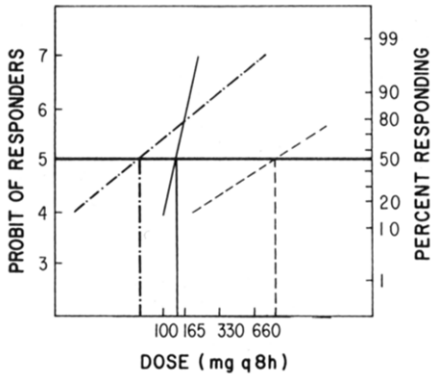


Table 4. Adverse Drug Effects in 15 Patients

Symptom	Quinidine Dose (mg every 8 h) 165 (n = 14) Pt No.	330 (n = 15) Pt No.	495 (n = 2) Pt No.	660 (n = 6) Pt No.
Nausea		5, 8		
Diarrhea		8	10	
Headache		11*†		15‡
Rash		4		9
Palpitation		3		11‡
Proarrhythmia		3		
QTc ≥ 500 ms		1		
Bradycardia < 30 beats/min		14		
Fever		8		
Cough	3*‡			
Insomnia	8*†			
Nervousness		11*†		
Dry mouth		11*†		
Eye swelling			2‡	
Bloating		4		

*On combination quinidine-mexiletine crossover limb; †probably mexiletine-related adverse effect; ‡unlikely related to quinidine or mexiletine. Pt = patient.

Long-term study. Ten patients continued taking combination quinidine-mexiletine after completing the dose-ranging protocol for a mean duration of 30 ± 26 weeks (range 4 to 87, median 24). Two patients continued taking quinidine after completing dose ranging, one for 44 weeks and the other for >85 weeks.

Discussion

Knowledge of the relation between drug dose and effect is the key to making rational dosage decisions. With many new antiarrhythmic agents, premarketing dose-ranging studies are performed to establish a reasonable initial dose. A basic principle is to start with the lowest dose likely to prove sufficiently effective. Recently, the U.S. Food and Drug Administration has encouraged premarketing strategies to define the low end of the dose-response curve. A major argument for investigating the low end of the dose-response curve is that because drug-related adverse effects increase as dose increases, the risk/benefit ratio also increases. Often for many drugs approved in the past, information concerning the low end of the dose-response curve is minimal, and for combination therapy, it may be altogether lacking.

Quinidine-mexiletine therapy versus quinidine monotherapy. In this crossover trial, the dose-response curve for quinidine-mexiletine was investigated and compared with that for quinidine monotherapy. The criteria of ≥80% sup-

JACC Vol. 15, No. 5
April 1990:1138–45

pression of ventricular premature complexes during combination therapy was reached in 13 of 14 patients compared with 5 of 15 during monotherapy. In addition, adverse effects occurred in 3 of 14 patients during combination therapy and in 10 of 15 during monotherapy. Adverse effects attributed to quinidine were frequent and occurred at even the lowest monotherapy dose. The quinidine dose used in combination with mexiletine to suppress ventricular premature complexes ≥80% in the combination limb was less than half that required in the monotherapy limb and significantly less than that previously reported (3,5,11). All patients except one responded at the lowest conventional quinidine dose in combination dictated by the protocol; however, it is theoretically possible that even lower quinidine or mexiletine doses could be effective (Fig. 3).

Comparison of quinidine-mexiletine dose with that in other studies. Previous studies (3–5) documenting the effectiveness of quinidine-mexiletine combination therapy utilized daily doses equivalent to or slightly less than that of conventional quinidine (200 to 400 mg every 6 h) or mexiletine (200 to 400 mg every 8 h) monotherapy. Two clinical studies (3,5) reported an average daily quinidine dose ranging from 824 to 1,080 mg. Another study (11) found the average daily quinidine dose to be 1,643 mg. Similarly, in these studies (3,5,11) the daily mexiletine dose was also high, ranging from 636 to 800 mg. In the present trial, daily doses were considerably lower (quinidine, 570 ± 87 mg; mexiletine, 450 ± 60 mg). Comparable suppression of ventricular premature complexes (88 ± 11%) and abolition of nonsustained ventricular tachycardia (100 ± 1%) with that in studies using higher doses was observed. One explanation for these findings is that the low end of the dose response for combination therapy is lower than previously considered. Another possibility is that our study patients differ from patients previously reported (3–5) in that they 1) predominantly have cardiomyopathy or electrical abnormalities; 2) have normal ejection fraction; 3) have benign or potentially malignant ventricular arrhythmias; and 4) had a 24 h ambulatory ECG rather than electrophysiologic testing to assess antiarrhythmic action.

Because the low end of the dose-response curve of combination therapy for malignant ventricular arrhythmias has not been studied, it remains to be evaluated whether doses similar to those used here can effectively suppress sustained ventricular arrhythmias. To date, no antiarrhythmic agent has been shown to reduce the incidence of fatal or nonfatal cardiac arrest; therefore, it is not known whether the administration of low dose quinidine-mexiletine, or any other antiarrhythmic drug, is clinically relevant. However, low dose quinidine-mexiletine may provide an alternative for patients who have symptomatic arrhythmias and find conventional or high doses of quinidine or mexiletine intolerable. Low dose quinidine-mexiletine combination therapy could also prove useful for patients with ventricular dysfunction in whom some antiarrhythmic therapy may further depress cardiac function. One report (11) indicates that daily doses of quinidine, 1,643 mg, plus mexiletine, 636 mg, do not depress left or right ventricular function at rest or during exercise. We anticipate that low dose quinidine-mexiletine would have a similar effect on ventricular function.

Although, a test of the efficacy of conventional mexiletine doses was not attempted here, in three earlier trials (12–14), conventional daily doses of mexiletine, 600 to 1,200 mg, suppressed arrhythmia in only 66% (12), 54% (13) and 69% (14) of patients with symptomatic ventricular premature complexes and ventricular tachycardia. Moreover, in each trial, the criterion for efficacy was lower (that is, 50% in one trial [12] as assessed with ambulatory ECG and exercise testing and 70% in the others [13,14]). Although the present trial did not have a mexiletine monotherapy limb, we used lower mexiletine doses than those the manufacturer recommends (15) or that have been extensively evaluated. Whether the more marked arrhythmia suppression during combination therapy could have been attributed solely to mexiletine, independent of low dose quinidine, was considered. Although this possibility seems somewhat unlikely in view of only moderate efficacy reported in previous studies (12–14) with conventional mexiletine monotherapy compared with >80% suppression in >80% of patients after low dose quinidine-mexiletine, further studies are required to test the efficacy of mexiletine, 100 to 150 mg three times daily.

Electropharmacologic effects. The electropharmacologic effects of combination quinidine-mexiletine have been extensively studied in a number of animal species (16–19) and humans (3–5). Studies of canine Purkinje fiber and rabbit ventricular muscle indicate that quinidine-mexiletine exerts a synergistic effect by depressing $\dot{V}_{max}$ to the same extent as solutions with twice the quinidine concentration (16) and prolongs refractoriness (17) and infarct zone conduction time (18) more than monotherapy. These basic electrophysiologic studies (16–19) support observations in humans (3–5), in whom combination therapy prolongs ventricular tachycardia cycle length and refractory periods and prolongs conduction in dyskinetic zones of the left ventricle. The changes in conduction and refractoriness seen with quinidine-mexiletine are thought to be consistent with the modulated receptor hypothesis (20), wherein an agent such as mexiletine provides added depression of early extrasystoles by blocking sodium channels not occupied by quinidine (21) vis a vis different kinetics of interaction with the sodium channel.

It has been suggested (3) that quinidine-mexiletine abolishes arrhythmias by prolonging conduction velocity in a reentrant circuit such that unidirectional block is converted to bidirectional block. Evidence for conduction delay is inferred from the ECG, on which prolongation of the coupling interval, as occurs with other type I agents such as procainamide (22), has been observed. However, prolonga-

tion of the coupling interval also occurred during quinidine monotherapy, providing an example of how a given arrhythmia, presumably produced by the same mechanism, responds more readily to a particular treatment or drug action. It is possible that quinidine might have suppressed arrhythmias to the same extent as combination therapy if additional drug could have been administered.

Conclusions. The issue of whether patients with frequent ventricular premature complexes and nonsustained ventricular tachycardia benefit from antiarrhythmic treatment with improved survival is not known. The recent disclosure from the Cardiac Arrhythmia Suppression Trial (CAST) (23) underscores difficulties in assessing such problems. In CAST, despite arrhythmia suppression, an adverse effect on survival and nonfatal cardiac arrest in postinfarction patients was observed after treatment with encainide or flecainide. Whether low dose quinidine-mexiletine therapy offers benefits for survival in addition to its significant antiarrhythmic action and modest incidence of adverse effects has not been evaluated. Further studies to evaluate the clinical relevance of low dose quinidine-mexiletine therapy in high risk patients will have to address the issue of improved survival. The observations presented here provide a rationale for further exploring low doses with combination therapy to achieve drug action and minimize adverse effects in symptomatic patients with benign ventricular arrhythmias.

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